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Review

Applications of nanotechnology in allergy and asthma

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Abstract

The increasing incidence of allergic diseases requires effective curative strategies for their alleviation. Allergen-specific immunotherapy (AIT) is a causal treatment technique instead of a symptomatic treatment technique for allergies. At present, AIT is being offered utilizing immunization response modifiers (IRMs) or adjuvants. The adjuvant helps in vigorous inaugral as well as long-term IR (immune response), thus enhancing the efficacy of AIT. The successful development of novel additives requires complete knowledge regarding the underdevelopment of novel and conservative additives. Hence, this review describes the applications of nanotechnology in allergic disorders, namely, allergies and asthma. The development of vaccines based on nanoparticles (NPs) is an important strategy for AIT because of their innate physicochemical characteristics, production ease and capacity to incite inherent immunity.

Keywords

Nanotechnology; Allergens; Immunotherapy, allergen-specific; Asthma; Adjuvants, immunologic

1. Introduction

Allergic disorders are believed to be an increasing health issue worldwide, affecting more than 25% of the population in developed states [1,2,3], and a considerable increase in the prevalence of allergic rhinitis (AR) and asthma has been observed globally since 1960 [1,4]. Currently, allergies are an important health care issue [5]. According to the World Health Organization (WHO), the majority of the world population (10–30%) experiences AR [6,7]. AR occurs due to IgE-mediated nasal mucosa inflammation. Patients present in outdoor and emergency departments with signs and symptoms of nasal blockage, nasal itching, watery rhinorrhea, sneezing, watery and red eyes, and psychosocial problems such as emotional distress, sleeping disorders, and financial losses due to absence from work [8]. AR is an important risk factor for asthma [5]. It is a respiratory disease that is characterized by spasms in the airway passages leading to difficulty breathing. This is usually due to the response to allergens and occurs in combination with other forms of hypersensitivity reactions. Asthma is a very common leading world health problem that affects more than 330 million people globally [9]; however, it is not curable despite decades of combined efforts to diagnose, treat, and prevent the disease in due time [10,11].

2. Immunotherapy for allergies and asthma

2.1. Immunotherapy

To treat allergies, immunotherapy is utilized extensively. Despite its efficiency, its fundamental mechanisms are incompletely understood. The purpose of immunotherapy is to 'act specifically' (AIT) to facilitate host desensitization to a particular antigen and, in other words, to make the host 'compatible' with the antigen. Therefore, a flourishing IT (immunotherapy) will cause an increase in the amount of allergen needed to encourage allergic indications, along with immediate- and late-phase reductions in allergic inflammation [12,13].

Various mediators are involved in allergic reactions (Figure 1). Therefore, it is advisable to deactivate them by using antagonists, for example, antihistamines, antileukotrienes or agonists of their cellular receptor, such as the β2 adrenoreceptor. However, this approach is not an ongoing therapeutic technique, and treatment must be repeated after every antigen encounter. In contrast, immunotherapy has an effect beyond therapy duration since immunotherapy changes the IR to antigens (Figure 2). IT decreases the Th1/Th2 ratio and encourages T effector regulatory cells. Such modifications in the global balance of T-cell subsets are shown in the enhanced formation of IL-10 by allergen-presenting cells, B cells and T cells, which, along with transforming growth factor beta (TGFβ) production, activate B cells to IgA (Immunoglobulin-A) and IgG4 (Immunoglobulin-G4) and repress IgE (Immunoglobulin-E) production [14]. IgA and IgG oppose IgE in terms of antigen binding, reducing antigen capture by basophils. Moreover, subsequent reactions or cascades after immunotherapy decrease the amount of mast cells, basophils, neutrophils and eosinophils at allergen exposure sites, resulting in a decrease in inflammatory indications. Allergies may be restricted to a systematic or organ (intestinal) involved in anaphylactic reactions. The engagement of various effectors and triggering elements should be measured during rational IT (Figure 3) [12].

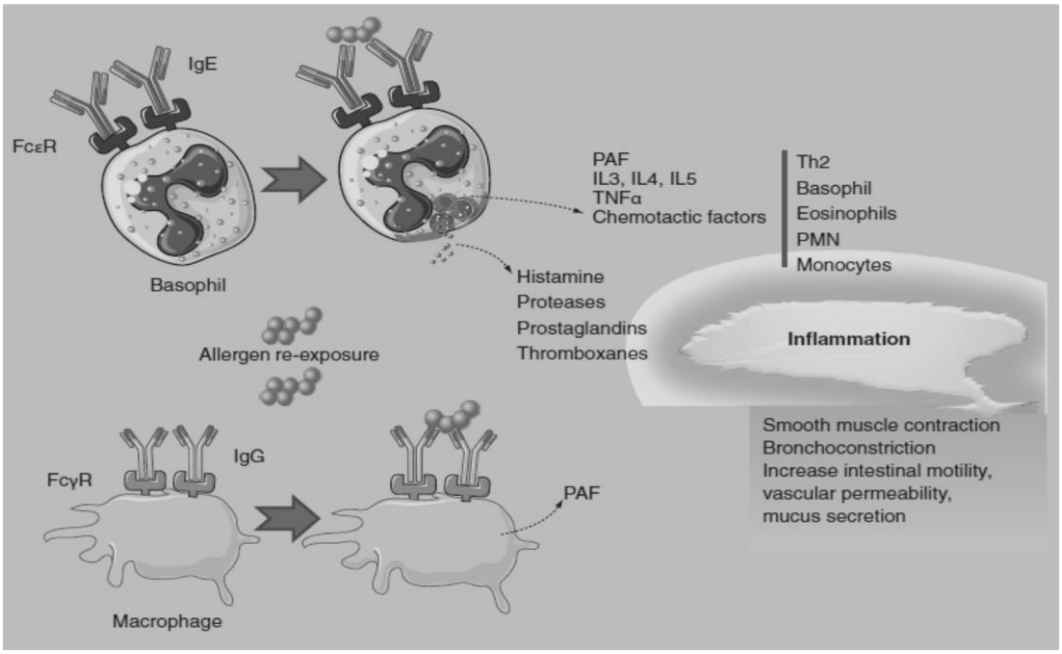

Figure 1. Allergy process.

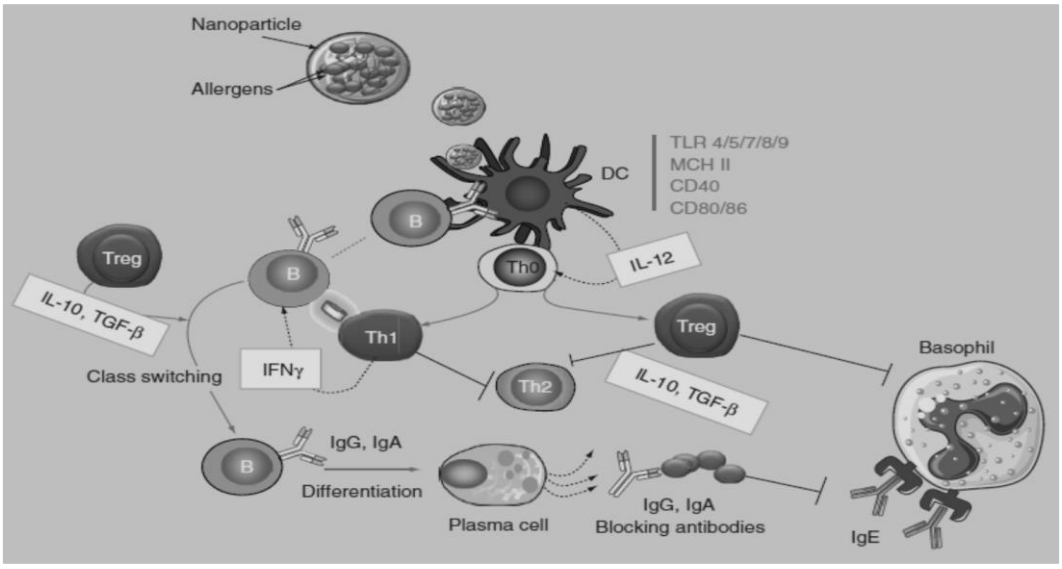

Figure 2. Immunization.

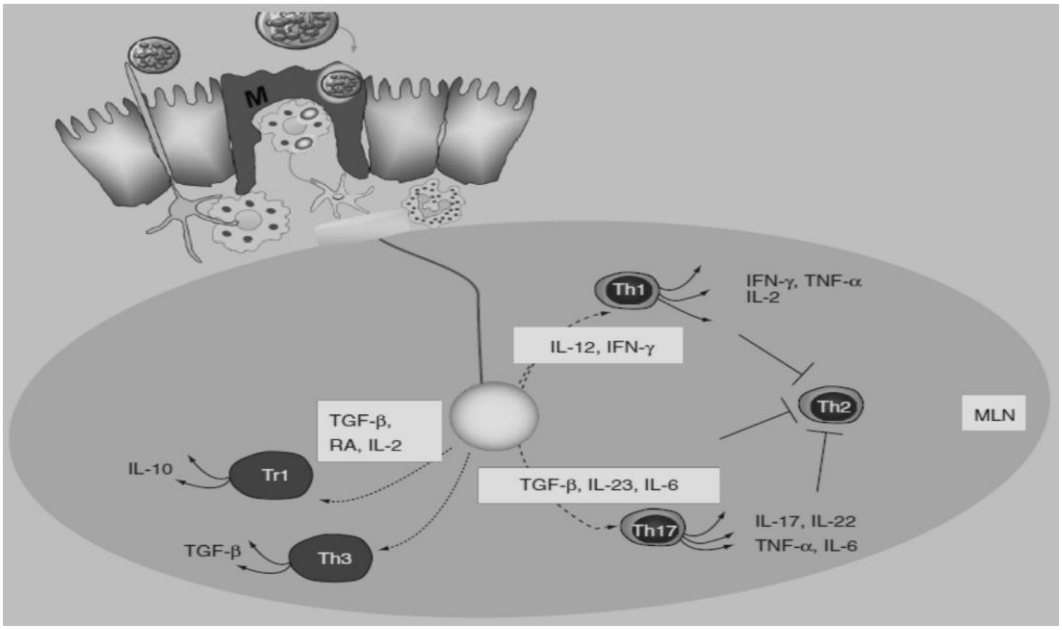

Figure 3. Oral immunotherapy.

Currently, traditional immunotherapy depends on immunization with repeated doses of allergens for durations imitating what the host feels while repeatedly confronting an ecological challenge. Therefore, after repetitive contact with 'substances' and to evade a constant inflammatory reaction, the host increases its regulatory reaction due to an increase in Tregs and Th1 cells, which represses immunoglobulin E production. However, despite these benefits, an insignificant proportion of patients opt for IT as their treatment option for allergies [15]. Subcutaneous immunotherapy, despite its effectiveness, is not limited due to possible side effects after immunization, such as local allergic reactions, infrequent anaphylaxis and even near-lethal responses [16,17]. Keeping in mind such risks, subcutaneous IT should be administered only by specialists. In contrast, to achieve continuing immunological reactions, it is necessary to obtain a minimum of 3 to 5 years of treatment, necessitating good patient compliance. An additional limitation regarding conventional subcutaneous immunotherapy is a phobia among a few patients

about needles and associated risks of needle use [18]. Thus, efforts to develop more convenient, safer and effective strategies are being explored, such as recombinant allergen generation that offers no IgE-mediated activation, novel adjuvants supporting particular Th1 responses, hypoallergenic glycoconjugates and, furthermore, various routes of specific immunotherapy (SIT) application, particularly sublingual, intralymphatic and epicutaneous delivery of antigens [19,20,21].

2.2. Mechanism of immunotherapy based on specific allergens

Allergen-specific immunotherapy (AIT) techniques are not fully understood. Recent studies have shown that efficient AIT successively activates several mechanisms and promotes molecular and cellular modifications (Figure 4) [22].

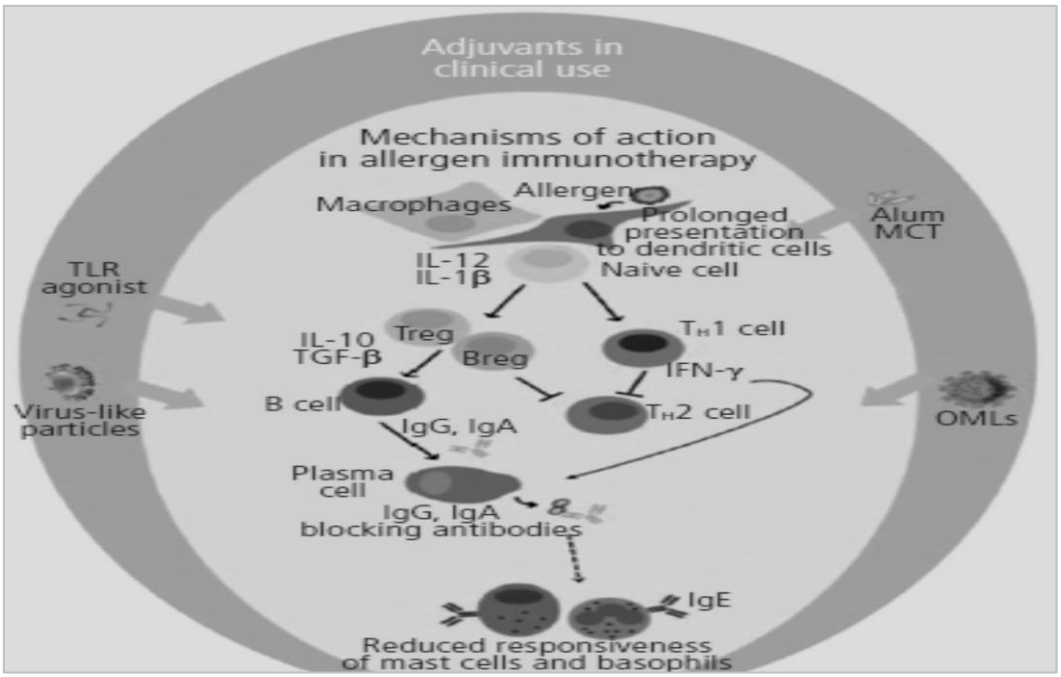

Figure 4. Allergan-specific immune therapy.

This complicated mode of action of AIT occurs in three phases: i) rapid desensitization, ii) early tolerance, and iii) sustained tolerance. This rapid desensitization is due to an initial decrease in the degranulation of basophils and mast cells, possibly caused by rapid upregulation of the histamine type 2 receptor. The 2nd phase, which is called early tolerance, comprises a reduction in interleukin-4 (IL-4)-releasing TH2 cells and an increase in interleukin-10-releasing Breg and Treg cells. A switch is found between TH1-type reactions and TH2-type reactions, with increases in interleukin-10 and TGFβ production. Moreover, there is an increase in Treg cells, which is associated with medical improvement. The final phase is sustained tolerance, in which Treg cells excite B cells to create allergen-specific immunoglobulin-G4, a tolerogenic elevated similarity blocking the antibody that competes with allergen-specific immunoglobulin-E, hence evading the allergen-induced secretion of the mediators through basophils and mast cells. These successively activated methods induce immune tolerance, which mitigates or even eliminates the allergic reaction in the early (acute) phase and any subsequent immunological events [22,23].

3. Applications of nanotechnology in allergies and asthma

3.1. Nanotechnology

Nanotechnology is believed to be an emerging technology because of the probability of making innovative products with total novel attributes and functions together with massive potential in a diverse variety of applications along with considerable impact on health care [24]. Nanotechnology is a multisectoral area of research that controls and manipulates molecules and atoms between 0.1 and 100 nm in size and manufactures relevant structures and materials [25,26]. As an influential motive for developing biomedicine, nanotechnology has expanded over the fields comprising early identification, prevention and treatment of diseases and bioengineering research, demonstrating hopeful prospects. The majority of nanomaterials (NMs) have been utilized in biomedical studies. Nanoparticles (NPs) are the most extensively studied medical delivery system and have been described in more than 25000 research articles during the last decade [27]. In 1995, the Doxil Nanotechnology (NT) platform was approved and became successful on the market. Since then, several nondrugs have also been approved by the Food and Drug Administration of the USA, while several other medicines are in clinical development [25].

3.2. Nanotechnology medicine applications

In medicine, the use of nanotechnology enhances the half-life of medications by enhancing drug incorporation, reducing drug degradation/clearance, and slowing the release of loaded drugs. The movement period of the nanoparticle body is controlled by the changing surface charge of the NPs, as per their application goal. However, a positive charge enhances the incorporation of NPs, and in the blood stream, negative charges increase the time of circulation. Additionally, they enhance drug bioavailability and increase the dissolvability of the hydrophobic preparation. They study pharmacokinetics and deliver medicines exactly as needed. Hence, they reduce the required dosages and side effects. They can be combined with one drug or more in combination. Decisions can be made autonomously by the new generation of nanorobotics according to circumstances and can assist surgeons during surgery [28,29,30,31,32]. The use of nanotechnology in medicine is summarized in Figure 5.

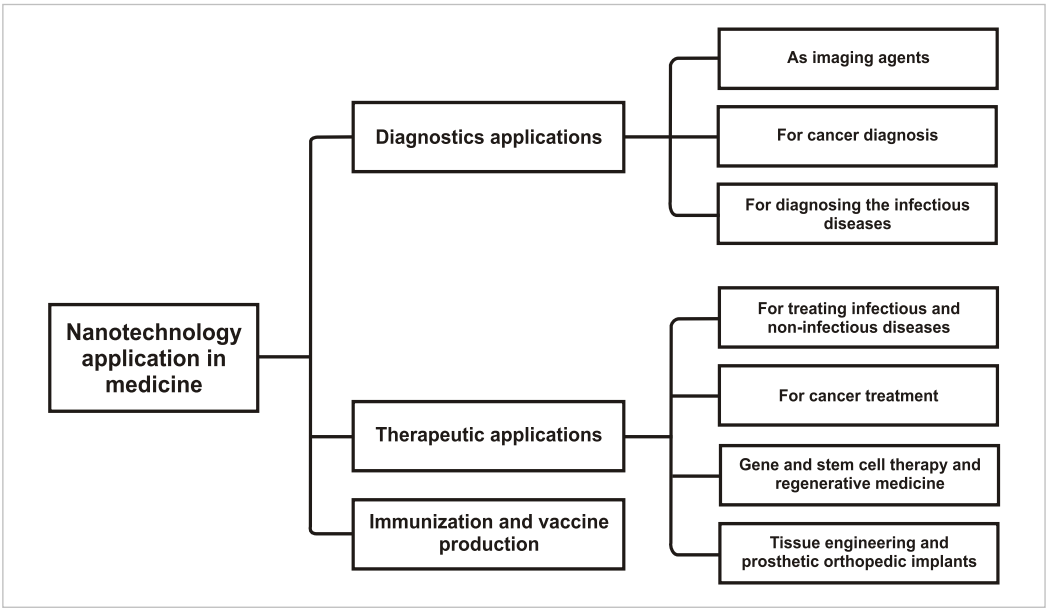

Figure 5. Overview of nanotechnology: applications of nanoparticles in the medical sciences, including immunization, therapeutics, and diagnostics.

3.3. Nanotechnology applied to immunotherapy

During the past decade, nanotechnologies have been utilized in immunomodulatory treatments to increase their effectiveness and to reduce possible side effects, mostly in addressing carcinoma and communicable diseases [1]. Over the past 30 years, numerous polymers have been utilized to design NPs that are able to load both nucleic acids and proteins for therapeutic applications [33,34]. However, no universally accepted NP definition is available that could be considered a basic component of NMs, having described physical boundaries and not less than one dimension/diameter in the nanoscale range [35]. In 2011, the definition of NMs suggested by the European Commission was based on size as a basic parameter to explain incidental, manufactured and natural materials having particles along with any external measurement in the "nano" range (1 to 100 nm) [36]. A very broad review, including current technological and scientific developments, is in progress [1].

NPs can take several different shapes and possess variable physical characteristics and chemical compositions, including size/hydrodynamic radius, surface chemistry, solubility, morphology and charge [37]. These characteristics could be exploited to make them appropriate for particular biomedical applications. The influence of physicochemical properties on NP biocompatibility is important for their use in biological applications and has been extensively investigated. In contrast, the biodistribution of NPs after they enter the human body through several routes, their cellular intake mechanisms and their probable toxicity are influenced mainly by the physicochemical characteristics of the particles, especially their surface and size characteristics [38].

3.4. Physical and chemical applications of NPs

Several physicochemical applications of NPs have been demonstrated to assist direct or indirect immune modulation. Short NPs can enhance tissue infiltration and thus increase the availability of particle-loaded allergens to lymph nodes and blood vessels [39]. The effects of transdermal administration of amorphous silicon dioxide were examined by Palmer and coworkers. In a model of allergic contact dermatitis, NPs were used, and they were found to have increased immunomodulatory potential. This research compares the epidermal patency of NPs to that of microparticles, indicating that NPs enhanced invasion (27.8 ± 3.4 nm) in mouse skin compared with microparticles (557.6 ± 35.1 nm) [40]. Similarly, Hirai and colleagues examined the epidermal penetration and subcellular localization of mono-dispersal silica in amorphous stat NPs 70 nm wide in rats and showed that the particles effectively invaded via epidemic barricades and were found in the lymph nodes present in local tissues [41]. Numerous studies have demonstrated the efficiency of injecting NPs into the epidermis barrier [42,43]. Good penetration and localization in tissue can actually enhance AIT through new administration routes, such as intranasal or percutaneous delivery. Moreover, their size, chemical composition, shape, solubility and surface charge make them appealing for AIT. Jatana and associates investigated the effect of the charge and size of various NPs (silica, silver, titanium dioxide and gold) on immunomodulation in a skin allergy mouse model and reported that negatively charged small NPs demonstrated immunosuppression [44]. Environmental polynameric NPs, which are biocompatible with cells and tissues, could be promising candidates for AIT because they could decrease unnecessary side effects related to the present therapy by utilizing alum as an additive. The nanoparticle surface and shape have a significant effect on cellular intake. Champion and teammates demonstrated in their study that one may control phagocytic intake through an effective structure. The authors found that globular particles are more effectively taken up by macrophages because of

their elevated length, as indicated by the normalization curve [45]. Particle surface properties can promote uptake by inducing communication with receptors on the cell surface (CRS). Hence, this characteristic can be utilized through nanoparticle surface functions with preferred active groups binding to particular receptors present on the surface. Lectin-functionalized polylactic-co-glycolic acid particles were suggested to be favorable platforms for oral AIT. This technique of functionalization was effective in selecting enterocytes, hence improving the uptake and preventing the degradation of the delivered allergen via gastrointestinal enzymes [46].

3.5. Depot-forming ability

The depot effect is believed to be a significant mechanism of immune tolerance induction. Prolonged and constant discharge of antigens can increase the exposure time of immune cells and can cause immunomodulation [47]. Furthermore, depot formation at the target site concurrently decreases the therapeutic dosage. In the case of NPs, the allergen can be summarized within carrying systems, while their discharge can be adjusted to the desired functions by adjusting the surface particle along with the polymer. The coating of chitosan on the encapsulating drug polylactic-co-glycolic acid NPs demonstrated a measured discharge of ingredients in pharmaceutical formulations that are active in comparison with that of pristine polylactic-co-glycolic acid NPs [48]. Lacey and colleagues highlighted an immune-increasing depot effect of cationic tuberculosis (TB) containing a liposome vaccine allergen (Ag85B–ESAT-6) [49]. Therefore, the ability of NPs to form a depot may have curative benefits [39].

3.6. Protection from enzymatic degradation

NPs can defend against antigens via encapsulation by protecting them from protease enzymes within the body, which is desired during oral immune therapy (OIT), similar to vaccines that have to overcome the harsh conditions of the gastrointestinal tract [50]. OIT is an innovative strategy under study for food allergy treatment. It was demonstrated to be effective for almost 60-80% of the populace investigated [51]. Brotons-Canto and colleagues examined the ability of mannosylated NPs for oral immunotherapy against peanut allergy in mice and found that AIT was highly suitable. From an innovative polymer, the NP system was synthesized by covalent binding of mannosamine to a polyanhydride backbone [52]. Similarly, OIT with polyanhydride NPs was shown to have significant advantages in peanut allergy therapy. A study showed an increase in Treg and Th1-resistant responses and a decrease in the activation of Th2 cells in in vivo mouse models. Srivasta and coworkers also demonstrated the success of preclinical research on oral immunotherapy utilizing CpG-coated polylactic-co-glycolic acid NPs in murine peanut allergy models [53]. The authors observed a significant and sustained reduction in the levels of peanut-specific IgE/IgG1, along with Th2 cytokines, as well as an increase in the levels of peanut-specific IgG2a and IFN-Ɣ. Additionally, this study investigated the safety of the use of CpG-poly(lactic-co-glycolic acid) NPs in oral immunotherapy by evaluating their inability to induce anaphylaxis by assessing the release of plasma histamine [53]. Therefore, the ability of NPs to prevent antigens together with the activation of the desired immune reaction enables them to be perfect for AIT [39].

3.7. Enhancement of allergen-specific tolerance

The ultimate goal of immunotherapy for allergic disorders is to increase tolerance to allergen-specific immune agents. The innate ability of NPs to target antigen-presenting cells and their ability to transmit signals, which evoke antigen-specific immune reac-

tions, make them feasible tools for modulating immune responses [54]. The NPs that can attain this objective of resistance tolerance induction can collectively be described as tolerogenic NPs. The application of AIT tolerogenic NPs would be suitable for preventing unnecessary immune reactions, which tend to occur in present therapeutic practice. Various sets of NPs have been used to induce tolerogenic immune reactions. Metalic oxide NPs, synthetic polymers and liposomes are being investigated; however, biodegradable polymeric NPs are the most commonly studied NMs [55,56]. Maldondo and collaborators reported the potential of a tolerogenic nanocarrier system (encapsulated with peptide protein/antigen) to neutralize and prevent a pathological resistance response [57]. Furthermore, polymeric NPs combined with CpG ODNs were confirmed to be efficient at treating allergic airway illness caused by house dust mites [58]. Nanoscale bronchial interventions combined with CpG markedly improved dendritic cell (DC) recruitment and initialization, causing Th1 immune resistance in a model of household dust mite allergy and decreasing allergy-associated indications. These studies certainly recommend further nanomaterial expansion as a potential platform technology to mitigate allergic diseases [39].

3.8. Nanoparticle therapy for asthma

Asthma occurs due to chronic airway inflammatory disorders related to airway hyperresponsiveness [59]. In asthma, chronic inflammation can cause ultrastructural modifications in airways related to airway remodeling. These modifications are incompletely transposed by recently available treatment strategies, such as steroids [60].

Asthma is thought to be best controlled by the use of steroid inhalation; however, the effects of this intervention are likely to be small, not >1–2 hours. Current research has demonstrated that stealth steroids compressed with NPs achieve high and prolonged benefits at airway inflammation sites compared with free steroids [61]. Moreover, budesonide NP agglomerates have shown an attractive microstructure for effective lung deposition, as do nanostructures for the swift dissolution of inadequately water-soluble drugs [62]. In addition, smaller NPs have more effective effects on bronchodilation [63]. Bhavna and associates (2009) highlighted that NPs compressed with salbutamol act together more with the lung layer, as mucociliary movement and peripheral deposition back to the tracheo-bronchial area are more severe, leading to higher and further sustained medicine concentrations within the target area [64].

During gene transfer, chitosan (a biocompatible cationic polysaccharide obtained from crustacean shell chitin) with an NP shape (100 to 200 nm) may be utilized to deliver plasmids. Kumar and colleagues (2003) indicated that chitosan interferon (IFN)-γ-plasmid deoxyribonucleic acid (pDNA) NP treatment successfully decreased functional and immunological anomalies related to antigen sensitization and challenge. This impact was primarily mediated through the STAT4 signaling pathway. Furthermore, due to similarities between humans and mice in terms of the T-cell demarcation pathway, these findings highlighted that chitosan IFN-γ-pDNA NPs could reverse allergic asthma in humans. Additionally, the outcomes obtained by Kumar and colleagues demonstrated that intranasal chitosan IFN-γ-pDNA nanoparticle treatment could be helpful in both prophylaxis and asthma treatment [65].

Additionally, Kong and Teammates (2008) reported that this treatment caused in situ production of IFN-γ, decreased airway reactivity and inflammation, decreased numbers of proinflammatory CD8+ T cells and inhibited antigen-presenting activity in dendritic cells in mice [66].

4. Conclusions

For AIT, a prospective vaccine should have the ability to achieve (i) efficacy and safety with an appropriate allergen dose, (ii) patient compliance, which is promoted through a well-tolerated regimen, self-administration, and cost-effectiveness, and (c) the minimization of adverse effects related to treatment. NPs can technically fulfill the abovementioned criteria, and their physiochemical properties and distinctive ability to induce immune tolerance might qualify them as an ideal type of adjuvant for AIT. Nanoparticle drug formulations offer numerous advantages over conventional formulations.

Thus, development in nanoscience will have a very significant impact because it has the potential to significantly transform healthcare in the coming years. Future studies and clinical trials are recommended to evaluate the exact role, efficacy, side effects and safety in the management of AR and asthma using robust new techniques.

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